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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,813	10/19/2004	Johannes Coy	4007.008	6538

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,813	COY, JOHANNES	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,36-38,45-50 and 65-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34, 36-38, 45-50, and 65-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 3/9/09 in response to the Office Action of 10/8/08 are acknowledged and have been entered.

Claims 71-72 have been added by Applicant.

Claims 34, 36-38, 45-50, and 65-72 are pending.

Claim 34 has been amended by Applicant.

Claims 34, 36-38, 45-50, and 65-72 are currently under examination.

The following Office Action contains NEW GROUNDS of rejections necessitated by amendments that changed the scope of the claims from methods of diagnosing individuals as having a disorder characterized by abnormal cell proliferation to methods of diagnosing an individual as having a cancer or "precancerous condition". Methods of diagnosing an individual as having a cancer or "precancerous condition" have not previously been considered.

Rejections Withdrawn

The previous rejection under 35 U.S.C. 112, first paragraph, is withdrawn.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34, 36-38, 45-50, and 65-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method for detecting carcinoma tissue in an individual comprising detecting in a tissue sample obtained from said individual the level of polynucleotides comprising SEQ ID NO:1 and comparing said level to the level of polynucleotides comprising SEQ ID NO:1 in a corresponding control tissue sample from a healthy subject, wherein a higher level of polynucleotides comprising SEQ ID NO:1 in the tissue sample from the individual as compared to said control tissue sample indicates that the tissue sample from the individual comprises carcinoma tissue, **does not reasonably provide enablement for** an in vitro method for detecting just any cancer and just any precancerous condition in an individual comprising detecting in a tissue sample obtained from said individual and a corresponding normal control levels of polynucleotides that hybridize to just any probe that has a sequence that is at least 80% identical to any part of at least 15 consecutive nucleotides of SEQ ID NO:1 or is complementary or reverse complementary to such a part and wherein said probe hybridizes under stringent conditions to SEQ ID NO:1 but does not hybridize to an other transketolase or transketolase like sequence, wherein a higher level of detected polynucleotides in the biological test sample as compared to the level of detected polynucleotides in the corresponding normal control indicates that said individual has just any cancer and just any precancerous condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to an in vitro method for detecting just any cancer and just any precancerous condition in an individual comprising detecting in a tissue sample obtained from said individual and a corresponding normal control levels of polynucleotides that hybridize to just any probe that has a sequence that is at least 80% identical to any part of at least 15 consecutive nucleotides of SEQ ID NO:1 or is complementary or reverse complementary to such a part and wherein said probe hybridizes under stringent conditions to SEQ ID NO:1 but does not hybridize to an other transketolase or transketolase like sequence, wherein a higher level of detected polynucleotides in the biological test sample as compared to the level of detected polynucleotides in the corresponding normal control indicates that said individual has just any cancer and just any precancerous condition. It is noted that probes encompassed by the claimed method are only required to comprise a sequence that shares as few as two consecutive bases with any 15 consecutive nucleotides of SEQ ID NO:1 or the complement thereof and wherein said probe hybridizes under stringent conditions to SEQ ID NO:1 but does not hybridize to an other transketolase or

transketolase like sequence. Further, the instant claims do not limit "stringent" conditions to any particular conditions. Therefore, the claims broadly include methods wherein the probe detects polynucleotides completely unrelated to SEQ ID NO:1 or the complement thereof. Further, this includes methods wherein just any cancer, including leukemia, is detected. Further, this includes methods wherein just any precancerous condition is detected. Because normal tissue is "precancerous", the claims encompass contradictory methods wherein higher levels of detected polynucleotides are indicative of cancer and normal tissue.

This invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology". Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The specification teaches an in vitro method for detecting carcinoma tissue in an individual comprising detecting in a tissue sample obtained from said individual the level of polynucleotides comprising SEQ ID NO:1 and comparing said level to the level of polynucleotides comprising SEQ ID NO:1 in a corresponding control tissue sample from a healthy subject, wherein a higher level of polynucleotides comprising SEQ ID NO:1 in the tissue sample from the individual as compared to said control tissue sample indicates that the tissue sample from the individual comprises carcinoma tissue (see Example 2, in particular). Carcinomas disclosed as overexpressing polynucleotides comprising SEQ ID NO:1 include those of colon, lung and stomach (see Example 2). The specification prophetically discloses performing the claimed method to detect non-carcinomas such as leukemia (see line 30 on page 20, in particular). However, the

specification does not demonstrate that polynucleotides comprising SEQ ID NO:1 are overexpressed in tissues other than the carcinoma tissue. Further, the specification does not demonstrate that polynucleotides comprising SEQ ID NO:1 functionally regulate carcinogenesis or are expressed as a result of a tissue becoming carcinomic. Further, the specification does not demonstrate that elevated levels of just any polynucleotide, other than transketolase or transketolase-like sequence, that hybridizes to a probe comprising a sequence that shares as few as two consecutive bases with any 15 consecutive nucleotides of SEQ ID NO:1 or the complement thereof and wherein said probe hybridizes under stringent conditions to SEQ ID NO:1 are indicative of caner or a precancerous condition.

The level of unpredictability for using a particular expression pattern of a particular molecule to detect any cancer or any pre-cancer is quite high. The state of the prior art dictates that one of skill in the art would not predict that a particular expression pattern of a particular molecule is indicative of a particular diseased state without a demonstration that said particular diseased stated correlates with said particular expression pattern of said particular molecule. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis

have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence demonstrating a particular expression pattern of a particular molecule correlating with a particular diseased state, one of skill in the art would not predict said particular expression pattern of said particular molecule correlates with said particular diseased state without undue experimentation. Experimentation to identify such a correlation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to an in vitro method for detecting just any cancer and just any precancerous condition in an individual comprising detecting in a tissue sample obtained from said individual and a corresponding normal control levels

of polynucleotides that hybridize to just any probe that has a sequence that is at least 80% identical to a part of at least 15 consecutive nucleotides of SEQ ID NO:1 or is complementary or reverse complementary to such a part and wherein said probe hybridizes under stringent conditions to SEQ ID NO:1 but does not hybridize to an other transketolase or transketolase like sequence, wherein a higher level of detected polynucleotides in the biological test sample as compared to the level of detected polynucleotides in the corresponding normal control indicates that said individual has just any cancer and just any precancerous condition, and Applicant has not enabled said method because it has not been shown that a higher level of detected polynucleotides that hybridize to any probe that has a sequence that is at least 80% identical to a part of at least 15 consecutive nucleotides of SEQ ID NO:1 or is complementary or reverse complementary to such a part and wherein said probe hybridizes under stringent conditions to SEQ ID NO:1 but does not hybridize to an other transketolase or transketolase like sequence is indicative of every cancer and every precancerous condition.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

In the Reply of 3/9/09, Applicant states that the claimed invention relates to a link between overexpression of TKT-F1 and disorders characterized by abnormal cell proliferation. Further, Applicant argues that no technical reason has been raised for the

Examiner to doubt that the claimed method is applicable to cancers other than carcinomas.

In regards to the statement that that the claimed invention relates to a link between overexpression of TKT-F1 and disorders characterized by abnormal cell proliferation, the claimed method is not limited to TKT-F1 overexpression and disorders characterized by abnormal cell proliferation. Rather, the claims broadly encompass methods of overexpression of any polynucleotides that hybridize to any probe that has a sequence that is at least 80% identical to any part of at least 15 consecutive nucleotides of SEQ ID NO:1 or is complementary or reverse complementary to such a part and wherein said probe hybridizes under stringent conditions to SEQ ID NO:1 but does not hybridize to an other transketolase or transketolase like sequence. Such probes would hybridize to numerous polynucleotides unrelated to SEQ ID NO:1, even under stringent conditions, because polynucleotides with relatively low homology to one another are able to hybridize under stringent conditions. Further, the instant claims do not limit "stringent" conditions to any particular conditions.

In regards to the argument that no technical reason has been raised for the Examiner to doubt that the claimed method is applicable to cancers other than carcinomas, Tockman et al teaches considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application (see above). In view of Tockman et al, absent evidence demonstrating a particular expression pattern of a particular molecule correlating with a particular diseased state, one of skill in the art would not predict said particular expression pattern of said particular molecule

correlates with said particular diseased state without undue experimentation. Further, one of skill in the art would recognize that the markers of carcinomas are not predictably markers of blood or bone marrow cancers such as leukemias because carcinomas arise from epithelial cells, while blood and bone marrow cancers such as leukemias arise from blood cells. Experimentation to demonstrate that a carcinoma marker is inductive on a blood or bone marrow cancer would in itself be inventive.

Summary

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Primary Examiner, Art Unit 1642